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ASTHMA AND HAY FEVER

Clinical Evaluation of Stock Respiratory Vaccine in the Treatment of Bronchial Asthma. Moore, M. W., and Reed, C. E.: Ann. Allergy **17**: 722, 1959.

The role which infection plays in the etiology of bronchial asthma is controversial from both the immunologic and clinical standpoints. The common association of upper respiratory infections with bronchial asthma and the familiar reproduction of symptoms by the injection of bacterial vaccines, the improvement of symptoms by use of antibiotic and bacterial vaccines all point to the fact that bacterial sensitivity may be a cause of certain human allergic disease states. There is considerable evidence which would indicate that this hypersensitivity is of the delayed type and an equal amount of evidence that it is of the immediate type. Whether it is one or the other, or a combination of the two, does not alter the clinical fact that bronchial asthma often follows and is closely associated with repeated upper respiratory infections and that treatment with bacterial vaccine frequently brings about improvement of the condition. Both autogenous and stock vaccines have been used for treatment, but the latter seems to give better results in most cases. This is probably due to the fact that autogenous vaccines do not cover as broad a spectrum of bacteria as do the stock vaccines, since all etiologic organisms involved may not have been present at the time the organisms for the vaccine were obtained.

Skin tests with bacterial proteins are not of much value in the diagnosis of bacterial asthma. In a series of 3,000 asthmatic patients that the author tested with autogenous and stock vaccines there was no difference in the reactions among those whose asthma was or was not associated with upper respiratory infections. It was also found that at the age of one year the skin reactions were almost always negative, but that with increasing age up to 40 years, the reaction became progressively larger. After the age of 40 the reactions remained about the same size. The diagnosis of bacterial asthma therefore can be made only on the basis of a thorough examination and a clinical history of repeated upper respiratory infections followed by asthma. Although the bacterial skin test is of no diagnostic importance its size may be employed as an indicator of the dosage which a patient believed to be bacterial sensitive should be able to accept. Vaccine injections should be given semi-weekly in gradually increasing doses until a maintenance level is reached, at which time the interval between doses is increased. Careful observation must be made for local or constitutional reactions and dosage adjusted accordingly. H. F.

An Evaluation of Hyposensitization in Childhood Allergy. Kline, A. H., and Waite, C. L.: Ann. Allergy **18**: 80, 1960.

A double blind study was employed to evaluate the therapeutic results of a desensitization program carried out in a series of 30 children suffering from respiratory allergies. The children were divided alternately at random into two groups, one of which was treated with injections of antigen and the other with placebo injections. After a period of 8 weeks of such a regime an evaluation of the results of treatment revealed that 11 (73.3 per cent) of the 15 children on anti-allergic hyposensitization therapy had complete abatement of symptoms and the remaining 4 were definitely improved. Of the 15 children who received placebo treatment, none showed complete disappearance of

symptoms, 4 showed some improvement, and 11 were unchanged. Following the 8-week period the children who had been on placebo injections were placed on appropriate antigen hyposensitization therapy. This brought about complete relief in 11 of the 15, marked improvement in 3 and no improvement in one. H. F.

A Preliminary Report on the Radiologic Evaluation of Trypsin in Certain Chronic Chest Diseases. Silbert, N. E.: Dis. Chest **35**: 162, 1959.

Three patients with severe chronic bronchial asthma complicated by bronchitis, bronchiectasis, and/or emphysema received 5 mg. trypsin daily for one week and then three to eight injections tapered over the next two or three weeks. X-ray films were taken before treatment, after 10 to 14 days, and then 6 to 8 weeks later. Inability to raise inspissated mucus was a requisite for inclusion in this series. In each case there was marked subjective improvement, and x-ray films, read by two independent radiologists, substantiated the clinical improvement in each case. E. W.

Trigger Mechanisms in Asthma. Overholt, R. H.: Dis. Chest **35**: 587, 1959.

Several groups of patients were considered as potential candidates for bronchographic study and pulmonary surgery. These groups included: (1) patients with intractable asthma whose illness was initiated by pneumonia; (2) patients with frequent chest "colds," productive cough, and unilateral wheezing; (3) patients with chest discomfort or pain, or some in whom there was systemic evidence of focal infection, such as arthritis. At laparotomy, the surgeon inspected and overhauled the defective or abnormally functioning ventilatory organ. He liberated abnormal anchored segments, divided adhesions or bands, decorticated constricted segments, removed enlarged nodes or destroyed segments, denervated a spastic lung and worked with it until all healthy segments were functioning properly. Among 31 patients followed for periods of 18 months to 12 years who were treated surgically in this manner, all were improved to some degree and three fourths of them significantly so. One half of the entire number treated were considered to be well and completely free of asthma. There were no hospital deaths among patients treated by this method. R. W.

MISCELLANEOUS ALLERGIES

Urticaria of the Gastric Mucosa With Massive Hemorrhage Following Oral Penicillin Anaphylaxis. Bralow, S. P., and Girsh, L. S.: Ann. Int. Med. **51**: 384, 1959.

An acute anaphylactic reaction with a massive gastrointestinal hemorrhage was observed in a 49-year-old penicillin-sensitive man following the ingestion of a single penicillin tablet. At the onset of the reaction the patient vomited dark red blood and had bright red bloody stools. Generalized urticaria did not develop. Limited upper gastrointestinal roentgenographic studies made the day after hemorrhage demonstrated an irregularity of the superior portion of the lesser curvature of the stomach which was suggestive of an ulcer. Absence of peristaltic activity and failure of the stomach to change contour suggested an infiltrative carcinomatous type of lesion. The next day, however, x-ray studies were normal and the gastric wall was pliable and distensible. One week after the original reaction, gastroscopy revealed the presence of thickened hyperemic antral mucosa, absence of peristalsis, one

hyperemic mass arising from the lesser curvature of the antrum and another at the cardiac end of the stomach. There was a loss of the normal rugal pattern at the cardia and bleeding could be seen along the greater curvature of the funnel end of the stomach. A third gastrointestinal series the next day was again normal except for some prominent rugal folds at the pylorus. Several days later air contrast studies failed to reveal any abnormalities and a repeat gastroscopy performed 20 days after the original episode was suggestive of only a mild superficial gastritis.

The changes noted in the stomach of this patient were similar to the gastric condition previously reported as localized angioedema of the gastric mucosa in human beings and were similar to those seen in dogs sensitized and shocked with horse serum. H. F.

Allergic and Toxic Reactions of Prolonged Chemotherapy for Pulmonary Tuberculosis. Fein, B. T.: Dis. Chest **36**: 286, 1959.

Among 100 patients with pulmonary tuberculosis, who developed reactions from prolonged chemotherapy, 17 were presumed to be allergic. Of these, 10 developed urticaria which appeared any time from 18 months to 36 months after the institution of therapy. Four patients developed angioedema from six months to twelve months after chemotherapy. Three of the patients had reactions which were described as anaphylactoid and which developed after 12 months of therapy in one patient, after 24 months of therapy in a second, and after 30 months of therapy in the third. These patients were receiving either streptomycin, para-aminosalicylic acid (PAS), and/or isoniazid (INH). It was apparent from these studies that the majority of allergic reactions developed after 18 months of therapy. Toxic reactions, of which 83 were encountered, usually developed earlier than 18 months. E. W.

Intradermal Reaction in Ancylostomiasis. Wei, P. H., and Kuo, N. K.: Chinese M. J. **76**: 556, 1958.

The value of the intracutaneous test in the mass diagnosis of hookworm infestation was studied. Three kinds of antigens prepared by two different methods were used. Antigen A was prepared from freshly expelled hookworms by pancreatic digestion. Antigens B and C were prepared by the usual saline extraction, Seitz filtration method. Extract B was prepared from freshly expelled worms, and Extract C from worms which had been preserved in 70 per cent alcohol for 3 years. Antigen and a saline control, sufficient to raise a wheal about 0.45 cm. in diameter, were injected intracutaneously on the forearm. Reactions were read in 15 minutes. Sixty patients with ancylostomiasis were tested with antigen A; fifty-eight (95.08 per cent) showed positive reaction. Fifty-two out of 55 patients (94.54 per cent) were positive to antigen B, and 21 out of 24 (87.5 per cent) were positive to antigen C. There were no positive reactions to antigen A when it was tested in 23 normal subjects. Three of 54 controls showed positive reactions to antigen B. All three of these subjects were found to have ascariasis. However, in the majority of ascariasis cases (11 out of 12), tests with antigen B showed negative reactions. It was concluded that the intracutaneous reaction elicited by hookworm extract is an aid in the diagnosis of ancylostomiasis and that it may be particularly useful in detecting the pre-adult stage of hookworm infestation or light infestations which might be missed on microscopic examination. T. Chao

PHARMACOLOGY, PHYSIOLOGY, AND PATHOLOGY

Effects of Exogenous Adrenocorticotropic Hormone (ACTH) Upon Pituitary ACTH Concentration After Prolonged Cortisone Treatment and Stress. Holub, D. A., Kitay, J. I., and Jailer, J. W.: J. Clin. Invest. **38**: 291, 1959.

The administration of exogenous ACTH to rats failed to prevent or ameliorate the depletion of ACTH observed in pituitary glands following a period of cortisone treatment. Adrenal atrophy secondary to steroid treatment was preventable by ACTH stimulation. Pituitary ACTH was measured by pooling pituitaries of groups of rats, extracting them, and assaying the ACTH content in a process involving incubation in vitro with rat adrenal slices. Values of ACTH for control and experimental groups were thus compared with each other and with a standard ACTH preparation. The depletion of ACTH was noted to be maximal 4 days after cessation of a 7-day course of cortisone. At 10 days following the course of treatment, ACTH levels were increasing but still significantly lower than control values. Adrenal atrophy at this time was still unrepaired, suggesting that ACTH synthesized during this period is stored, not secreted. Rats given ACTH and cortisone concurrently seemed to have slightly greater concentrations of ACTH in their pituitaries.

Rats were subjected to a scalding stress; pituitary ACTH in untreated scalded rats fell to 34 per cent of the values obtained in control animals prior to stress. Cortisone-treated animals subjected to stress showed over 50 per cent decrease from the already lowered pre-stress levels of pituitary ACTH. Animals treated with both ACTH and cortisone concurrently showed significant reduction in pituitary ACTH resulting from stress, comparable to that seen in rats given cortisone alone. In contrast, when ACTH administration continued past the cortisone treatment period to within 24 hours of stress, pituitary ACTH was not diminished. It is suggested that exogenous ACTH inhibits the release of ACTH from the pituitary gland at the time of stress. Exogenous ACTH failed to raise pituitary ACTH concentrations in cortisone-treated rats in contrast to the rise noted in normal and adrenalectomized rats in earlier publications by the same authors. "Exogenous ACTH apparently is unable to reverse the steroid-induced inhibition of ACTH synthesis and depletion of ACTH stores." E. K.

Immunological Studies in Nephritis. Freedman, P., and Markowitz, A.: Lancet **2**: 45, 1959.

Frozen slices of kidney tissue from patients with glomerulonephritis, lupus nephritis, and polyarteritis nodosa were eluted in a citrate buffer solution for 90 minutes and then stained with anti-gamma-globulin fluorescein conjugate. A comparison of these sections with untreated sections similarly stained with the conjugate showed a definite though slight diminution in specific fluorescence following elution of the tissue. Examination of the eluates by electrophoretic and immunological techniques revealed the presence of gamma-globulin. Studies on glomeruli isolated from normal and diseased kidney tissue, by fluorescent antibody techniques, demonstrated glomerular localized gamma-globulin in the glomerulonephritic and lupus kidney, but not in the normal kidney. A marked diminution of specific fluorescence was noted when sections of these tissues were eluted in citrate buffer. In order to identify further the glomerular localized globulin, the biologic activity was studied by layering the eluates on frozen sections of various human kidneys, including

sections of kidney from which the glomeruli had been isolated. Staining the sections, before and after the application of the eluates, with fluorescent anti-human gamma-globulin made it possible to determine whether specificity existed. The gamma-globulin isolated from the glomerulonephritic glomeruli did not demonstrate any affinity for these tissues. In some tissue preparations, however, the lupus globulin appeared to increase the fluorescence in the glomerular wall and in Bowman's capsule. The addition of fresh normal serum to globulin obtained from glomerulonephritic glomeruli did not alter its specific affinity for kidney tissue. The addition of the fresh normal serum to the gamma-globulin isolated from lupus glomeruli did, however, increase its affinity for all cell nuclei. Tissue affinity was not demonstrated by the eluate obtained from normal kidney, either by itself or in the presence of fresh normal serum. The factors in fresh serum which facilitated the attachment of the lupus gamma-globulin to cell nuclei were destroyed by heating to 60° C. for 3 minutes. This lupus globulin in the presence of fresh normal heat-inactivated serum behaved identically as pure lupus globulin. Further studies suggested that a serum factor, distinct from albumin and from alpha 1, alpha 2, beta and gamma-globulin, reacting immunologically as complement, may be present in the glomeruli of kidneys from patients with glomerulonephritis and lupus nephritis. Complement may be the factor in serum which potentiates and alters the affinity of globulin for specific kidney tissue, but in the absence of a pure preparation of human complement further confirmation must be obtained. R. W.

Relationship of Stress-Induced Histidine Decarboxylase to Circulatory Homeostasis and Shock. Schayer, R. W.: Science **131**: 226, 1960.

Previous studies have demonstrated that the activity of the adaptive mammalian enzyme, histidine decarboxylase, increases in response to nonspecific stress. In view of the known release of catechol amines in response to stress, the effect of these agents on histidine decarboxylase activity was investigated. Mice, injected intramuscularly with either epinephrine in oil or oil alone, were sacrificed 6 hours later and the tissues were assayed for histidine decarboxylase activity. The activity found in the mouse skin and lung increased approximately fourfold in the epinephrine-treated animals as compared to the controls. The activity in the skin of treated mice appeared to reach a peak 6 hours after injection and returned to approximately control levels in 24 hours. When animals were treated with three injections of norepinephrine and tested for histidine decarboxylase activity six and one-half hours later, the skin revealed a threefold increase in activity. When the dose of norepinephrine was tripled, a fivefold increase in the skin activity resulted.

These observations suggest that a balance may exist between the two catechol amines on the one hand, and newly synthesized histamine on the other. If during stress the supply of either histamine or catechol amines fails, the remaining amine may be very toxic to the cells of the small blood vessels and cause shock. B. S.

Effect of the Valsalva Experiment Upon Arterial pCO_2, O_2 Saturation, and pH in 45 Patients With Obstructive Pulmonary Emphysema. Smith, R. B., and Hatch, H. B., Jr.: J. Lab. & Clin. Med. **53**: 686, 1959.

A Cournand needle was inserted into the brachial artery of one arm of 45 patients with varying degrees of obstructive pulmonary emphysema and

blood was collected in specially prepared syringes. The first sample was collected with the patient at rest. A second sample of blood was obtained while the patient, after inhaling the maximal amount of air, maintained a modified Valsalva experiment with oral pressure ranging between 40 and 80 mm. Hg; this second sample was obtained between the sixth and twelfth seconds of maintenance of pressure. The third sample was obtained immediately after the standard exercise test with a suitable rest period between the modified Valsalva experiment and the exercise test. All patients had the usual ventilatory tests. The O_2 and pCO_2, contents and the pH of the blood samples were determined. In the 45 patients with varying degrees of obstructive pulmonary emphysema, three types of changes in the pCO_2, O_2 saturation, and pH of the arterial blood were observed. In patients with only minimal pulmonary disease, the response to the Valsalva experiment paralleled the normal. There was a rise in arterial O_2 saturation to between 96 and 100 per cent from the normal resting level of between 93 and 96 per cent. A precipitous fall in the pCO_2 occurred to as low as 23 mm. Hg from the normal resting level of approximately 40 mm. Hg. A shift of the pH of the arterial blood was noted to the alkaline side of normal, proportionately with the fall in pCO_2. Two thirds of the 45 patients showed this normal pattern. The remaining patients showed one of two types of abnormal patterns. In one type there was a decrease in both arterial O_2 saturation and in pCO_2, and a rise in pH. In the other type, there was a decrease in arterial O_2 saturation with a rise in pCO_2 and a fall in pH. It was postulated that the modified Valsalva experiment was of prognostic value in determining the degree of pathologic changes present in the pulmonary parenchyma of individuals suffering with obstructive pulmonary emphysema. These changes were irreversible if the arterial O_2 saturation failed to rise above the resting level during performance of the Valsalva experiment. On the other hand, if, with the Valsalva experiment, the arterial O_2 saturation increased above the resting level, it was believed that the pulmonary disease had not reached the stage of irreversible destruction and that use of proper breathing exercises, expectorants, and bronchodilators could be expected to improve both the ventilatory and respiratory functions. E. W.

A Survey of the Serum Protein Electrophoresis Pattern in Allergic Children.
Dees, S. C., and Grunt, J. A.: Ann. Allergy **18**: 50, 1960.

Serum protein electrophoresis patterns were determined in 283 allergic children (170 boys and 113 girls) ranging in age from 4 months to 14 years. Age, sex, allergic diagnosis, presence of infection, isoagglutinin level, and skin reactions were all compared and related to the serum protein pattern.

The distribution of the values found in the allergic group was comparable to those previously reported for normal children. Furthermore, there was no characteristic pattern which could be related to any specific allergic disease. Sex and age had no apparent influence on the values of any of the protein fractions and there was no significant relationship between the values for each component of the serum protein and the presence or absence of infection. There were, however, certain patients with infection in whom the gamma globulin level was below the mean for their age. A comparison of the isoagglutinin titers and the mean gamma globulin, as well as the range of gamma globulin for the various allergic diseases, failed to show any significant differences. There was no obvious variation in the gamma globulin level in children with isoagglutinin titers either above or below normal and there was no consistent relationship between titer and age.

A comparison of skin tests with the mean gamma globulin level indicated a tendency for the lower gamma globulin values to be associated with the weaker skin reactions and the slightly higher values with the stronger skin reactions. H. F.

Pulmonary Transcapillary Exchange of Na^{24} and P^{32}-Labeled Phosphate in Pulmonary Emphysema. Rothschild, M. A., Davis, A. L., Oratz, M., and Schreiber, S. S.: J. Clin. Invest. **38**: 2224, 1959.

Emphysematous patients and hospitalized persons without hematologic or cardiopulmonary disease were given intravenous injections of Na^{24} and albumin I^{131}, or P^{32}-labeled phosphate and albumin I^{131}. At two-second intervals blood was withdrawn from the brachial artery. The albumin was used for reference purposes because the capillaries are relatively impermeable to this substance. In studying the ascending portion of the curves (before a re-entry of isotope into the circulation could take place), the mean net loss of Na^{24} was 3.8 per cent in 7 emphysematous patients while the mean loss for 11 controls was 12.9 per cent. When P^{32}-labeled phosphate was injected, no loss was found in 3 of the emphysematous patients and the mean loss for the 6 emphysema cases studied was 2.6 per cent. Six controls showed a loss of 11.4 per cent. "Although it is recognized that no final conclusions as to the mechanism may be drawn, the fact remains that electrolyte transfer as measured here is markedly reduced emphysema." E. K.

IMMUNOLOGY

The Antibody Response of Lymph Node Cells Transferred to Tolerant Recipients. Weigle, W. O., and Dixon, F. J.: J. Immunol. **82**: 516, 1959.

Sensitized lymph node cells, when transferred to animals made immunologically unresponsive by x-radiation, are capable of making a secondary antibody response when challenged with the sensitizing antigen. Unsensitized normal lymphoid cells when transferred to similarly treated hosts are incapable of making a primary antibody response to serum protein antigens in their new environment. Whether it was the cell transfer or the unfavorable milieu of the radiated host which prevented the primary response was still undetermined. For information on this question the results of cell transfer obtained in recipients made tolerant to serum protein antigens by exposure at birth were compared with those obtained in x-radiated recipients.

Lymphoid cells were obtained from donor rabbits which had been hyperimmunized with bovine serum albumin (BSA) or bovine gamma globulin (BGG), and from normal donor rabbits. These cells were transferred to x-radiated recipient rabbits and to animals made tolerant to these antigens by repeated injection during neonatal life. Immediately after cell transfer both groups of recipients were injected intravenously with I^{131} tagged antigen. The sera of the recipients were then studied for the elimination of the tagged antigen and the appearance of precipitin antibodies. When BGG- or BSA-tolerant recipients were injected with related sensitized cells and tagged antigen they completely eliminated the antigen within 4 days with the subsequent appearance of antibodies in the sera. Of 15 tolerant recipients receiving unsensitized cells and tagged BGG, eight showed complete disappearance of antigen within 8 days. In 2 of these recipients, antibody could be detected 3 days after the antigen had been eliminated. Immune elimination of antigen or antibody response did not take place after 14 days in x-radiated recipients injected with unsensitized cells and tagged antigen.

The more rapid elimination of antigen in the animals receiving sensitized cells as compared to those receiving normal cells conformed with the secondary and primary responses seen in normal intact rabbits.

The immune elimination of antigen observed in 8 out of 15 of the tolerant recipients receiving unsensitized cells, and the subsequent antibody response in 2 of the animals, were not unusual findings and resembled the results obtained in normal rabbits immunized with similar amounts of antigen. Homograft rejection of transferred cells in some recipients may have contributed to their failure to eliminate antigen completely. Homograft rejection occurs from 7 to 9 days after transfer of cells. Primary response takes 10 to 14 days in a normal rabbit, hence may have interfered with a primary antibody response in some tolerant recipients.

X-radiation produces a condition in which the recipient appears to be unfavorable for a primary response by transferred normal lymph node cells, but it does not prevent the completion of a secondary response by cells sensitized prior to transfer. The milieu of the tolerant host does not prevent either primary or secondary antibody responses by transferred cells but the tolerant animal seems per se to be incapable of antibody response probably because of some cellular factor. It is suggested that the cells responsible for the recognition of antigens and/or production of antibody were the sites of unresponsiveness in rabbits tolerant to soluble protein antigens. D. Stein

The Relationship Between Delayed Hypersensitivity and Circulating Antibody Induced by Protein Antigens in Guinea Pigs. Sell, S., and Weigle, W. O.: J. Immunol. **83**: 257, 1959.

Guinea pigs sensitized by injection of bovine gamma globulin (BGG) immune precipitates in adjuvant were studied for the purpose of correlating the time of onset of delayed and Arthus type reactions with the appearance of circulating antibody and the immune elimination of antigen.

Guinea pigs received foot pad injections of BGG-anti-BGG precipitates in adjuvant, which had been prepared in antibody excess. The elimination of BGG labeled with I^{131} administered intramuscularly was used as an indicator of antigen elimination and as one measure of antibody production. Skin tests were done only in some of the animals and never more than once since it was found that their performance affected the course of subsequent delayed reactions. Skin test reactions were read at 5, 24, and 48 hours. Hemagglutination and anaphylactic tests were also used as methods of testing for circulating anti-BGG.

Delayed reactions tended to appear about the fourth day, increasing in amount to day 7, and declining to control levels by day 16. As the delayed reaction started to decline after day 7, the 5-hour reading became more prominent, reaching a typical Arthus type of appearance on day 12. In some animals the delayed type of reaction subsequently reappeared again. The immune elimination of antigen began on about day 7 when the delayed reaction tended to be at its maximum. Elimination of antigen was usually complete by day 11 when the 5-hour reaction was reading its maximum. By the 12th day hemagglutination tests and evidence of anaphylactic sensitivity became strongly positive. The intravenous administration of soluble antigen to the sensitized animals tended to block the appearance of delayed reactions.

The immune elimination of circulating antigen seemed related to the presence of circulating antibody and not dependent on cellular sensitivity. Thus, the injection of protein antigen–antibody complexes in adjuvant may

lead not only to delayed sensitivity but also to the production of circulating antibodies. However, it is still not clear whether there are two metabolically separate immune responses involved or whether they are part of a single process. B. S.

Complement-Fixing Autoantibody to Thyroglobulin in Hashimoto's Disease. Anderson, J. R., Goudie, R. B., and Gray, K. G.: Lancet **1**: 644, 1959.

The sera of 53 patients with Hashimoto's disease were tested for their ability to react with thyroglobulin by means of precipitin and complement-fixation tests. Nine sera were found to show complement-fixation reactions with nontoxic thyroid extracts as well as with thyrotoxic extracts. Further investigation of four of these sera revealed that there were apparently two different types of complement-fixating antibodies; one type reacted with thyrotoxic antigen only and the other reacted with both thyrotoxic and non-thyrotoxic extracts. Complement-fixation titrations with various thyroid extracts were performed on a 1-2 dilution of one of these sera. Colloid goiter extracts were found to have a slightly higher antigenic titer than thyrotoxic extracts, especially if the thyrotoxic extracts came from glands with a low colloid content because of prior treatment with potassium perchlorate before surgery. Complement-fixation tests with this serum and a solution of human thyroglobulin gave a reaction pattern similar to that obtained with nontoxic extracts. Control tests with normal serum and Hashimoto sera containing only thyrotoxic complement-fixation (C.F.) antibody or precipitin antibody, however, were negative. Fractionation of extracts by means of electrophoresis gave further evidence that the antigen producing the above reaction was thyroglobulin. Precipitin formation produced by mixing the above serum with nontoxic thyroid extract, followed by redissolving the precipitate with increasing quantities of complement, showed obvious increased fixation of complement by the precipitate. Hashimoto's sera, which contained precipitins and thyrotoxic C.F. antibody, but no thyroglobulin C.F. antibody, following exposure to nontoxic extracts, yielded precipitates which were essentially lacking in C.F. properties. Three other sera which were thoroughly investigated were similarly shown to fix complement with a solution of purified thyroglobulin. Previously two distinct antibodies were shown to be associated with thyroid disease. One of these reacted with thyroglobulin and was demonstrable by the precipitin reaction as well as by the tanned red cell agglutination technique, while the other reacted with a constituent of thyrotoxic thyroid tissue and was demonstrable only by the complement-fixation reaction. It is suggested that a third antibody may be present in Hashimoto's serum which reacts with thyroglobulin (nontoxic thyroid tissue) to fix complement. The exact significance of this antibody is yet to be determined. R. W.

Investigations of Thyroid Antigens Reacting With Hashimoto Sera: Evidence For an Antigen Other Than Thyroglobulin. Belyavin, G., and Trotter, W. R.: Lancet **1**: 648, 1959.

Thyroid antigens were prepared from normal thyroids or thyrotoxic glands. The crude minces and homogenates of normal glands usually gave uniformly negative results when checked for complement-fixing antibodies with sera from cases of Hashimoto's disease, whereas homogenates of thyrotoxic glands removed at surgery gave strongly positive reactions with Hashimoto antiserum. These results were obtained even in the absence of a

detectable gel precipitation reaction. In contrast, agar-gel preparations disclosed gel-precipitating sera which reacted with antigens derived from either normal or thyrotoxic glands. Studies were carried out on 206 sera obtained from patients with various forms of thyroid disease and with 36 sera from a variety of nonthyroid conditions. The complement-fixation test was positive in 51 of 64 cases of Hashimoto's disease, 10 of 19 cases of myxedema, and 28 of 66 cases of thyrotoxicosis. There was no correlation between the complement-fixing potency of the sera studied and the quantity of thyroglobulin present in the extracts of the normal or thyrotoxic glands. Complete removal of antibody against thyroglobulin by means of absorption with semi-purified thyroglobulin did not affect the complement-fixing potency of the serum against thyrotoxic complement-fixation (TCF) factor. Studies of the molecular size of the TCF factor were carried out by differential centrifugation, according to the method of Schneider. The TCF factor was found in the "microsomal" fraction, suggesting that it is probably an intracellular substance. The centrifuged deposits with high complement-fixation activity contained no detectable thyroglobulin and only traces of iodine, indicating that TCF factor and thyroglobulin can be separated. The possible significance of these findings is discussed. R. W.

Antibody Response to Intracutaneous and Subcutaneous Influenza Vaccination. Stille, W. T., Woolridge, R. L., and Gundelfinger, B. F.: J. Lab. & Clin. Med. **53**: 751, 1959.

One hundred and sixty-eight naval recruit volunteers were inoculated with varying amounts of Asian influenza virus vaccine by either the subcutaneous or intracutaneous routes. This vaccine contained about 800 CCA units per milliliter and was used either undiluted or diluted 1:10, 1:100, and 1:10,000. Blood samples were taken prior to inoculation and 21 days later, and both sera were titrated "blind" in a single hemagglutination inhibition (HI) test and again using the complement-fixation (CF) test. A one milliliter formalinized saline inoculation was given subcutaneously to a control group. Since the HI and CF antibody titers tended to be proportional in all aspects, only the former were discussed in this report. It was found that the intracutaneous route of vaccine administration was accompanied by a superior antibody response with dosage of about 50 CCA units per milliliter or less. With vaccine of more than 50 CCA units per milliliter, in amounts of 1 ml. subcutaneously or 0.1 ml. intracutaneously, the subcutaneous route was superior. Monovalent inoculations of more than 50 CCA units tended to result in relatively greater antibody production when given by the subcutaneous route. These studies suggested that the relation between the logarithm of the dose and the antibody response is linear in the case of the intracutaneous route and curvilinear (or sigmoid in the case of the subcutaneous route). It was concluded that the differences noted by other investigators, favoring one or the other routes of vaccine administration, were in part due to variation in the vaccine potency and biologic differences between the two routes of vaccine administration. E. W.

Antigenicity of Connective Tissue Extracts. Heller, P., Yakulis, V. J., and Zimmerman, H. J.: Proc. Soc. Exper. Biol. & Med. **101**: 509, 1959.

Male guinea pigs were sensitized with extracts of connective tissue prepared from leg tendons of young and aged rabbits mixed with equal amounts of Freund's adjuvant. Blood for immunological study was obtained by

cardiac puncture 10 days after the last of 4 subcutaneous or intramuscular injections. When 31 guinea pigs were immunized with connective tissue extracts of aged rabbits, complement-fixing antibodies of high titer developed in the majority of animals. Low titers were found in the 32 animals sensitized with young connective tissue. Similar results were found with gel precipitin tests. Controls injected with Freund's adjuvant or with rabbit serum alone yielded no antibody to connective tissue extracts. Groups of guinea pigs were sensitized with the cytoplasmic and nuclear fractions of rabbit leukocytes. Cross reactions between connective tissue antisera and leukocyte cytoplasm were noted by complement fixation and precipitin tests. There was no cross reaction between connective tissue antisera and nuclear antigen. The chemical characteristics of the antigenic component of connective tissue were discussed. The reason for antigenic differences between the connective tissue extracts of aged and young rabbits remains obscure.

T. Chao

Physiochemical and Immunologic Studies of Gamma Globulins of Normal Human Urine. Franklin, E. C.: J. Clin. Invest. **38**: 2159, 1959.

Human urines were found to contain protein with electrophoretic mobility similar to that of serum gamma globulin. The proportion of this fraction relative to other protein present was higher than in the corresponding serum. Ultra centrifugal study revealed that this gamma globulin fraction "appears to be one-fifth to one-sixth the size of the serum gamma globulin, and has a sedimentation coefficient of approximately 1.6 S." Precipitation occurred when the gamma globulin was studied against an antiserum to normal human gamma globulin, both with capillary and double diffusion techniques. Antisera to urinary gamma globulin fractions showed results confirmatory of the existence of a high degree of cross-reaction between the gamma globulins of urine and serum.

Four human subjects were injected intravenously with I^{131} labeled gamma globulin. Approximately two-thirds of the radioactivity excreted in the urine was found in the gamma globulin fraction and 10 per cent had migrated with the albumin fraction. Free I^{131} added to human serum in vitro was used as a control. It appeared that the 7 S gamma globulin in serum probably gave rise to the corresponding smaller fractions in urine. The mechanism by which these small sized gamma globulins reach the urine is discussed. E. K.

Leukocyte Agglutinins. II. Electrophoretic Separation of the Agglutinating Fraction. Wilson, H. E., Rheins, M. S., Naegeli, S. A., and George, W.: J. Lab. & Clin. Med. **53**: 863, 1959.

In order to identify the source of leukocyte-agglutinating factors, sera to be tested were fractionated in a continuous flow paper electrophoresis cell. The fractions were identified by standard paper strip electrophoresis, were then dialyzed, lyophilized, and tested for leukocyte agglutinins, employing a slight modification of the usual technique. Seventeen sera were fractionated and tested for leukocyte agglutinins. Of these, ten were positive and seven were negative for leukocyte agglutinins when tested as whole serum. In all of the ten sera from six agglutinin-positive patients, the activity was present in the zone corresponding to the gamma globulins, but not in other fractions. Conversely, similar studies of the fraction of negative sera and those of pooled normal serum and of multiple myeloma failed to reveal any leukocyte agglutinating activity in any of the fractions obtained. E. W.

Effects of Total-Body Irradiation on the Production of Antibody in Man. Stoloff, I. L., Haurani, F. I., Repplinger, E. F., and Havens, W. P., Jr.: New England J. Med. **260**: 1258, 1959.

The immunologic responses to diphtheria toxoid of 6 patients with acute leukemia and one patient with disseminated neuroblastoma were studied following varying doses of radiation and infusion of human bone marrow. The patients, who ranged in age from 5 to 41 years, had all been given antimetabolites in the past and were receiving appropriate supportive therapy, including whole blood transfusions, during the period of study. Forty-eight hours after whole body irradiation and subsequent infusion of healthy human bone marrow, the patients were tested and found to be Schick-negative. They were then given intramuscular booster injections of specific amounts of purified diphtheria toxoid.

Bone marrow cells for infusion were furnished by 9 healthy donors, 7 of whom gave histories of having received a complete course of active immunization against tetanus. Two to 13 days before the cells were transferred to the irradiated patients, the donors were inoculated with tetanus toxoid. Before and during the period of study, blood samples from the patients were tested for circulating diphtheria antitoxin and tetanus antitoxin, and those from the donors were studied for circulating tetanus antitoxin. Patients receiving from 170 r to 290 r total body radiation apparently had no alteration in their immunologic responses either quantitatively or qualitatively. Large amounts of antitoxin were produced when circulating neutrocytes and lymphocytes were less than 50 per cubic millimeter of blood. Data on two patients receiving 800 r suggested delayed or suppressed production of antibody but were inconclusive. These 2 patients lived only 7 and 14 days, respectively, after injection of toxoid. There was no apparent relationship between the capacity for antibody production and the degree of alteration of blood elements, resistance to infection, or survival after radiation. Attempts to demonstrate the production of tetanus antitoxin by the infused normal marrow cells in the irradiated host were unsuccessful. H. S.

Autoantibodies Against Spermatozoa in Sterile Men. Rumke, P. H., and Hellinga, G.: Am. J. Clin. Path. **32**: 357, 1959.

In a study of 2,015 husbands who came to a sterility clinic, 67 were found to have blood serum spermagglutinins in titers of 1:32 or more. Of 416 husbands of pregnant women, 4 had sperm agglutinins in titers of 1:4 to 1:16. Three types of agglutination were observed, head-to-head, tail-to-tail, and mixed. Tail agglutination sometimes specifically affected the tip of the tail and sometimes affected the mid-portion. "The type of autoagglutination of the semen was always similar to the type observed when normal spermatozoa were added to the serum of the patient." The agglutinin resisted heating for 30 minutes to 56° C.; it could be absorbed by packed spermatozoa; it moved in the gamma globulin fraction of the serum on paper electrophoresis; it could be eluted from the washed sediment of ejaculate. The agglutinin titer was higher in serum than in seminal fluid. Sperm agglutinins do not cross-react with erythrocytes, leukocytes, or thrombocytes, and sera from patients with antibodies against various blood cells or mumps virus failed to agglutinate sperm. One observation indicated that agglutinated sperm were unable to penetrate cervical mucus. In 17 testicular biopsies of men with sperm agglutinins, 15 disclosed normal spermatogenesis indicating that the agglutinin does not affect spermatogenesis. Evidence is presented that continued spermatogenesis in the presence of occlusion of efferent ducts provides an important mechanism for formation of spermagglutinins. E. K.

OTORHINOLOGY AND OPHTHALMOLOGY

A Study of the Nasal Cytology in Infants With Eczemoid Dermatitis. Crawford, L. V.: Ann. Allergy **18**: 59, 1960.

Nasal cytologic studies were performed on 85 infants, ranging in age from 5 to 24 months, with atopic, seborrheic, or contact eczema. Infants with a clinical history or with physical findings suggestive of an associated allergic rhinitis or asthma were not included in this study. Fifty nonallergic and noneczematous infants served as controls. Three serial nasal smears were obtained from each infant by use of a sterile, dry, soft rubber bulb syringe. Slides were stained according to the method of Hansel. A smear was regarded as positive if eosinophils were present in clumps or if they constituted over 10 per cent of the cells in any one of the three specimens. The infants were examined at 2 to 8 week intervals over a period of 2 years for the development of allergic rhinitis or asthma. Nasal smears were also done at biweekly intervals for a period of 5 months on 50 additional newborn nonallergic infants.

Twenty-six per cent of the 50 newborn infants gave positive smears for eosinophils on at least one examination. After the nursery period the incidence of nasal eosinophilia in these infants decreased until at 3 months only one showed a positive smear for eosinophils. In the eczematous group, the nasal secretions were positive for eosinophils in 52 per cent of the atopic eczemas, in 10 per cent of the seborrheic eczemas, and in 7 per cent of those with contact eczema. Four per cent of the normal controls had at least one positive smear.

The two-year follow-up revealed that 62 per cent of the atopic group progressed to respiratory sensitization while none of the children with seborrheic or contact eczema developed such symptoms. Four per cent of the 50 control infants developed respiratory allergy. It was noted further that 85 per cent of the atopic group, with positive nasal smears, developed nasal allergy while the incidence was only 37 per cent in those with negative smears.

These findings seemed to indicate that nasal eosinophilia is a common but not abnormal finding in infants under 3 months of age; however, in older infants it might be of value as a criterion for classifying an eczematoid dermatitis as allergic. Nasal eosinophilia in this age group of infants can also be helpful in predicting the development of allergic respiratory conditions. H. F.

Tonsillectomy and Allergy. Lerner, M. F., and Markow, H.: New York J. Med. **59**: 2888, 1959.

The authors reviewed the case histories of 70 allergic patients who had undergone tonsillectomy prior to treatment in the allergy clinic. At the time of tonsillectomy 50 patients manifested clinical symptoms of allergy and 20 patients had no evidence of active allergic disease. Among the latter group of patients, 50 per cent obtained relief from sore throats and high fever after tonsillectomy but all developed clinical symptoms of allergic disease within a period of 1 to 12 years; 8 in the group developed asthma. Tonsillectomy improved only 2 of the 50 patients with active allergic symptoms, each of whom was already under continuous allergic management prior to surgery. Seven other allergic patients obtained temporary improvement; 16 were unchanged and 33 were either made worse or developed new allergies within a period of 3 years. Of the 57 nonasthmatic patients who underwent surgery,

16 developed asthma following the tonsillectomy, including 8 of the group of 20 patients who were not clinically allergic prior to surgery. The possible consequences of performing tonsillectomy on allergic patients are discussed. R. W.

ANAPHYLAXIS

Tissue Electrolyte Changes in Anaphylactic Shock. Nelson, C. T.: Arch. Dermat. **79**: 444, 1959.

Approximately 70 per cent of mice sensitized intraperitoneally to horse serum experienced total anaphylaxis 30 to 45 minutes following an intravenous challenging dose. Tissue samples of muscle, viscera, skin, and bone removed from the shocked animals immediately after death showed an elevation of the electrolyte values of potassium, sodium, and chloride in muscle and viscera, whereas bone had an increase in sodium and chloride with a decrease in potassium. Bone was found to lose calcium which was replaced by sodium. The injection of cortisone 6 to 48 hours prior to the challenging dose of antigen completely protected the animal from fatal anaphylaxis for at least 3 days. Hormone-treated animals remained desensitized or immune to another challenging dose of antigen for a period of at least 7 to 10 days, thus demonstrating that the hormone did not prevent union of antigen and antibody. In the cortisone-protected animals, the increase in the electrolyte content of the muscle, skin, viscera, and bone was less than that found in unprotected mice dying in shock. Pretreatment with corticotropin had little effect in preventing fatal anaphylaxis; however, pretreatment with 11 desoxycorticosterone markedly increased the percentage of animals that died in fatal shock. Neither ACTH nor deoxycorticosterone, administered prior to shock, produced depression in tissue electrolytes characteristic of pretreatment with cortisone.

The author also studied the effects on anaphylaxis of hydralazine (Apresoline), Regitine, epinephrine, norepinephrine, serotonin barbiturates, tranquilizers, and a serotonin antagonist (lysergic acid diethylamide-LSD), anti-inflammatory drugs such as salicylates, phenylbutazone, and several new steroids such as hydrocortisone, prednisone, prednisolone, and fluorocortisone. All the steroids were found to be as effective as cortisone in preventing anaphylaxis but lysergic acid diethylamide, which blocks the action of serotonin, had less protective action. Tranquilizers with antiserotonin properties, such as reserpine and chlorpromazine, if given in sufficient dosage to produce good sedation protected mice against anaphylaxis almost as well as cortisone. All the drugs which inhibited anaphylaxis in mice acted by altering the electrolyte changes which followed the union of antigen and antibody and not by preventing the union of antigen with antibody. R. W.

Quantitative Studies of Repeated Cutaneous Anaphylaxis at Sites Sensitized With a Single Injection of Antibody. Rosenberg, L. T., Chandler, M. H., and Fischel, E. E.: J. Immunol. **83**: 264, 1959.

In guinea pigs, cutaneous sites passively sensitized with a single injection of guine pig antibody were found to react more than once to separate intravenous injections of small amounts of antigen. Four hours after intracutaneous sensitization the animals were challenged intravenously. They were rechallenged again at 24 hours after sensitization with antigen containing Congo Red or Evans Blue dye. Reactions were read 10 minutes after each challenge. When the primary challenge was carried out with a large

amount of antigen, a second reaction was rarely elicited on repetition of the challenge. With small initial challenging doses, reactions were almost regularly elicited on second challenge. Third reactions, at 48 hours after sensitization, could be elicited at times if the quantities of sensitizing and challenging doses were carefully controlled. B. S.

MISCELLANEOUS

The Lack of Absorption of Ingested Bovine Antibody in Humans. Dixon, F. J., Kuhns, W., Weigle, W. O., and Taylor, P.: J. Immunol. **83**: 437, 1960.

A quantitative study was made of the absorption of bovine antibody in cow's milk and serum from the gastrointestinal tracts of normal human newborn infants and adults.

Three courses of diphtheria toxoid injections were given to a cow beginning in the third month of lactation and extending over a seven-month period so that by the end of the third course the serum diphtheria antitoxin (DAT) level was 480 units per milliliter and the level in the milk whey was 1 per cent of that in the serum. Milk and serum were then fed for 3 days to three groups of subjects: ten 1-day-old term infants, three two- to three-month-old unimmunized children, and eleven Schick-positive medical students. Post-ingestion serum from the subjects was subsequently tested for DAT by the rabbit skin neutralization test, and by hemagglutination titrations. The sera were also tested for the presence of bovine gamma globulin by the Ouchterlony technique.

The experimental results indicated that insignificant amounts of DAT and bovine gamma globulin were absorbed via the human gastrointestinal tract from ingested hyperimmune cow's milk and serum. No more than 0.01 to 0.03 per cent of the ingested DAT was present in the serum of the recipients. Similar results were also obtained when colostrum from the same cow was fed to newborn infants. It is concluded that little or no passive immunity with bovine antibodies can be achieved by oral administration in human beings.

D. Stein

Problems Associated With Aspiration of Grass Heads (Inflorescences). Clery, A. P., Ellis, F. H., Jr., and Schmidt, H. W.: J. A. M. A. **171**: 1478, 1959.

Grass heads, such as the inflorescences of timothy, barley, oats, sandbur, and cattail may be aspirated into the lungs, especially by children who tend to "smoke" grass. A series of 14 cases are described. The early symptoms following aspiration are severe and alarming and consist of choking, coughing, cyanosis, and gagging. An asthmatoid wheeze is almost an invariable symptom. Pneumonitis develops often within 24 hours and may be followed by chronic pulmonary disease. Hemoptysis is a common sign. Some inflorescences such as timothy are nonextrusive and remain fixed in the bronchus. Others like oats and barley have stiff spikelets which act like the barbs of a fish hook. These tend to be carried further into the lung tissue and eventually reach the outside through a sinus. Immediate bronchoscopy is indicated in all cases. If unsuccessful, early thoracotomy is advisable since occasionally a fatality may occur. M. C.